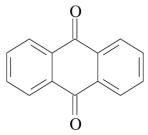
Toxicology and Carcinogenesis Studies of Anthraquinone-TR494



ANTHRAQUINONE

CAS No. 84-65-1

Background Information

- The 2-year carcinogenicity study of anthraquinone was conducted with material manufactured by oxidation of anthracene in acid; this was the highest purity material available. The material contained a contaminant present at 0.1% that was not identified.
- After peer review but prior to finalization of the draft report, the NTP was advised that bioassay material was mutagenic in bacteria, and that the mutagenicity was due to the 0.1% contaminant, identified as 9-nitroanthracene, a mutagen.
- Anthraquinone lacking the contaminant was not mutagenic in bacteria.
- Anthraquinone manufactured by Friedel-Crafts or Diels-Alder based processes does not contain 9-nitroanthracene and are not mutagnic in bacteria.
- Therefore the NTP and others performed additional work to determine the potential impact of the contaminant on interpretation of the studies.

Additional studies Conducted by NTP

- Evaluated the mutagenicity of bioassay material subject to further purification to remove the 0.1% contaminant
- Evaluated the bacterial mutagenicity of 9-nitroanthracene
- Identified the urinary metabolites of the anthraquinone used in the bioassay and manufactured by manufactured FC or DA
- Evaluated the mutagenicity of the major urinary metabolites of anthraquinone
- Evaluated the bacterial mutagenicity of the anthraquinone sample used in the bioassay
- Evaluated the bacterial mutagenicity of anthraquinone produced by the Friedel-Crafts and Diels-Alder manufacturing processes

Quantity of 1-, and 2-Hydroxyanthraquinone in the Urine of F344 Rats Administered Anthraquinone in Feed.

Anthraquninone Sample	Total Eliminated (µg/24 hrs.)	
	7500 ppm	3750 ppm
1-Hydroxyanthraquinone		
control	0	0
Acid oxidation	26.18	8.25
Diels-Alder (K)	55.18	15.162
Diels-Alder (E)	64.44	19.07
Friedel-Crafts (E)	53.84	26.53
2-Hydroxyanthraquinone		
control	0	0
Acid oxidation	1162.98	399.52
Diels-Alder (K)	2893.23	636.6
Diels-Alder (E)	2224.80	819.5
Friedel-Crafts (E)	2730.48	1057.26
9-Nitroanthracene potentially available	138(theoretical)	69(theoretical)

NTP Mutagenicity Results

Chemical	TA98	TA100
ANQ-pbio	(-/-)*	(-/-)
9-NA	(+/+)	(w+/+)
1-OH-ANQ	(-/-)	(-/-)
2-OH-ANQ	(+/+)	(-/-)
ANQ-bio	(-/-)	(-/-)
ANQ-DA1 ANQ-DA2	(+/+) (-/-)	(w+/+) (-/-)
ANQ-FC	(-/-)	(-/-)

*(-S9/+S9)

Comparison of Mutagenicity Results

Chemical	NTP	Butterworth
ANQ-bio	TA98(-/-)* TA100(-/-) TA1537(-/-)	TA98(+/-) TA100(-/-) TA1535(-/-) TA1537(+/-) WP2uvrA(-/-)
ANQ-pbio	(-/-)	(-/-) All Strains
ANQ-DA	(+/+)	(-/-) All strains
ANQ-FC	(-/-)	(-/-) All Strains
9-NA	TA98(+/+) TA100(w+/+)	TA98(+/-) TA100(+/-)
1-OH-ANQ	(-/-)	TA1537(-/+)
2-OH-ANQ	TA98(+/+) TA100(-/-)	TA100(-/+) TA1537(-/+)

*(-S9/+S9)

2-Hydroxyanthraquinone

- Major urinary metabolite of ANQ regardless of the method of manufacture.
- Is a bacterial mutagen.
- Is produced in situ from absorbed anthraquinone.
- Is present at several fold higher concentration than is theoretically possible for 9-nitroanthracene (assuming 100% absorption and bioavailability for the latter).
- Formation in the liver and elimination in urine would result in significant exposure to the liver and kidney, major target organs in this study.

Conclusions

- The mechanisim involved in anthraquinone carcinogenesis is not known.
- The use of "anthracene-derived" provides sufficient latitude to conclude that anthraquinone produced by other methods would not be carcinogenic.
- The NTP recommends that the name of the report be "Studies of Anthraquinone" and not "Studies of Anthracene-derived Anthraquinone":

Mutagenicity Results Reported by Butterworth

Chemical	TA98	TA100	TA1535	TA1537	WP2uvrA
ANQ-bio	(+/-)*	(+/-)	(-/-)	(+/-)	(-/-)
ANQ-pbio	(-/-)	(-/-)	(-/-)	(-/-)	(-/-)
ANQ-DA	(-/-)	(-/-)	(-/-)	(-/-)	(-/-)
ANQ-FC	(-/-)	(-/-)	(-/-)	(-/-)	(-/-)
9-NA	(+/-)	(+/-)			
1-OH-ANQ	(-/-)	(-/-)	(-/-)	(-/+)	(-/-)
2-OH-ANQ	(-/-)	(-/+)	(-/-)	(-/+)	(-/-)

*(-S9/+S9)